52. The method of claim 1, wherein said prodrug is activated in said patient through natural processes and is subject to detoxification by conversion to an intermediate of lower toxicity, and said enzyme is capable of reconverting the detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site.

## REMARKS

Applicants thank Examiner Saunders for the courtesy of an interview held in his office on July 9, 2001.

Claims 2-11, 21-29 and 31-50 have been cancelled, and claims 51-52 have been added. Claims 1, 16-20 and 30 have been amended. Accordingly, claims 1, 12-20, 30 and 51-52 are pending. In compliance with 37 C.F.R. § 1.121(b & c), Applicants enclose marked up versions of the amended claims and pages 26, 27 and 29, showing all of the relative changes.

Support for these amendments can be found throughout the specification and, in particular, the original claims.

## I. OBJECTIONS

The Examiner objects to Figure 3 for missing the "l" of "light chain." Applicants assert that replacement Figure 3, provided herein, obviates the objection.

The Examiner also requested that the status of referenced applications be updated. Applicants assert that the proposed amendments to the specification obviate the objection.

The Examiner objects to the lack of a sequence listing since the specification contains sequences with four or more amino acids. Applicants concurrently submit herewith a sequence listing in compliance with 37 C.F.R. §1.821-1.825 and assert that the objection has been obviated.

## II. STATUTORY DOUBLE PATENTING

The Examiner provisionally rejects claims 1-4, 6-10, 12-20, 25-27, 30, 32-34 under 35 U.S.C. §101 for allegedly claiming the same invention as copending Application No. 09/382,186. Applicants assert that the subject matter of the amended claims differs markedly from that claimed in Application No. 09/382,186. Accordingly, Applicants respectfully request that the rejection be withdrawn.

## III. OBVIOUSNESS-TYPE DOUBLE PATENTING

The Examiner provisionally rejects claims 5, 11, 21-24, 28-29 and 31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 and 25-28 of copending Application No. 09/382,186. Applicants assert that the subject matter of the amended claims differs markedly from that claimed in Application No. 09/382,186. Accordingly, Applicants respectfully request that the rejection be withdrawn.

## IV. REJECTIONS UNDER 35 U.S.C. §112, ¶2

The Examiner rejects claims 16-29 under 35 U.S.C. §112, ¶2, for allegedly being indefinite. Applicants respectfully traverse the rejections.

Applicants believe that one skilled in the art would understand the meaning of the claims in the context of the invention. First, the functionality of the claimed components is not relevant to the determination of whether one skilled in the art would understand the breadth of the claimed invention. Claims 16-19 are directed, respectively, to targetable conjugates of claim 1 that comprise a peptide, a carbohydrate, one or more haptens, and one or more chelators or metal-chelate complexes. Applicants submit that an artisan would recognize readily that the scope of the invention extends to targetable conjugates having any of the claimed elements.

Second, the specification provides that a targetable conjugate of the present invention comprises a carrier portion which comprises or bears at least one epitope recognized by at least one arm of a bi-specific antibody or antibody fragment, wherein, preferably, a hapten comprises the epitope. *See* Application, page 9, lines 30-33. The specification further discloses that in the alternative the epitope can be a part of the carrier. *See* Application, sentence spanning pages 9 and 10. Accordingly, Applicants assert that one skilled in the art, in light of the specification, would understand the relationship of the claimed components to the conjugate defined in Claim 1. Therefore, Applicants respectfully request that the rejection be withdrawn.

The Examiner also rejects claims 28 under 35 U.S.C. §112, ¶2, for allegedly being indefinite. As claim 28 has been canceled, the rejection is now moot.

## V. REJECTIONS UNDER 35 U.S.C. §102

The examiner rejects claims 1, 9, 16, 18-20, 32 and 34 under 35 U.S.C. §102(a), for allegedly being anticipated by Gautherot *et al.*; claims 1, 3, 9, 12-16, 18-19, 24-29 and

32-34 under 35 U.S.C. §102(a), for allegedly being anticipated by Karacay *et al.* (*Proceedings of the American Association for Cancer Research Annual Meeting*)("Karacay I"); claim 30 under 35 U.S.C. §102(a), for allegedly being anticipated by Karacay *et al.* Karacay I; claims 1, 3, 9, 12-16, 18-19, 24-30 and 32-34 under 35 U.S.C. §102(a), for allegedly being anticipated by Karacay *et al.* (*J. Nuc. Med.*)("Karacay II"); claims 1, 9, 16, 18-19, 32 and 34 under 35 U.S.C. §102(b), for allegedly being anticipated by Bardies *et al.*; claim 30 under 35 U.S.C. §102(b), for allegedly being anticipated by Gautherot *et al.* or Bardies *et al.*; claims 1, 3, 6-7, 9-10, 12-13, 16, 18-19, 32 and 34 under 35 U.S.C. §102(b), for allegedly being anticipated by Barbet *et al*; claim 30 under 35 U.S.C. §102(b), for allegedly being anticipated by Barbet *et al.*; and claims 1, 3, 6-7, 9, 12-13, 18-19, 30, 32 and 34 under 35 U.S.C. §102(b), for allegedly being anticipated by Goodwin *et al.* Applicants submit that proposed claim amendments obviate the rejections.

None of these references teaches methods of treating diseased tissues in a patient, comprising administering to the patient a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate, administering to the patient a first targetable conjugate which comprises a carrier portion and one or more conjugated enzymes, wherein the carrier portion comprises or bears at least one epitope recognizable by the at least one other arm of the bi-specific antibody or antibody fragment, and administering to the patient a second targetable conjugate which comprises a carrier portion and a prodrug, wherein the carrier portion comprises or bears at least one epitope recognizable by the at least one other arm of the bi-specific antibody or antibody fragment. Accordingly, Applicants respectfully request that the rejections be withdrawn.

## VI. REJECTIONS UNDER 35 U.S.C. §103(a)

The examiner rejects claim 30 under 35 U.S.C. §103(a), for allegedly being unpatentable over Gautherot *et al.* or Bardies *et al.*; rejects claim 30 under 35 U.S.C. §103(a), for allegedly being unpatentable over Karacay I; claims 1, 9 and 11 under 35 U.S.C. §103(a), for allegedly being unpatentable over Barbet *et al.* or Goodwin *et al.*, either in view of Griffiths; claims 1, 14-15 and 32-33 under 35 U.S.C. §103(a), for allegedly being unpatentable over Bardies *et al.*, Gautherot *et al.*, Barbet *et al.*, or Goodwin *et al.*, any in view of Goldenberg; claims 1 and 8 under 35 U.S.C. §103(a), for allegedly being unpatentable over Barbet *et al.* or Goodwin *et al.*, either in view of

Kondratyev; and claims 1 and 20 under 35 U.S.C. §103(a), for allegedly being unpatentable over Barbet *et al.* or Goodwin *et al.*, either in view of Huston *et al.* The examiner also provisionally rejects claims 1 and 4-5 under 35 U.S.C. §103(a), for allegedly being unpatentable over copending Application No. 09/205,243 in view of Barbet *et al.* or Goodwin *et al.* Applicants submit that the claim amendments herein obviate the rejections.

None of the cited references teaches or suggests the claimed methods. Furthermore, no combination of these references would lead one of reasonable skill in the art to the claimed invention. Moreover, there is no evidence that the skilled artisan would have been motivated to combine the references. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984)(*stating* that the mere fact that the prior art can be combined or modified does not render the combination obvious unless the prior art suggested the desirability of the modification). Accordingly, Applicants respectfully request that the rejections be withdrawn.

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In view of the foregoing remarks it is believed that the application is in condition for allowance. A favorable disposition of the application therefore is solicited. Examiner Saunders also is courteously invited to contact the undersigned if any questions remain or if he believes that further discussion will advance prosecution.

Respectfully submitted,

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MARKED UP VERSION OF CLAIM AMENDMENTS

1. (Amended) A method of treating **[or identifying]** diseased tissues in a patient, comprising:

(A) administering to said patient a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate;

(B) optionally, administering to said patient a clearing composition, and allowing said composition to clear non-localized antibodies or antibody fragments from circulation;

(C) administering to said patient a first targetable conjugate which comprises a carrier portion **and one or more conjugated enzymes, wherein said carrier portion [which]** comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment**[, and one or more conjugated therapeutic or diagnostic agents, or enzymes]**; and

(D) **[when said targetable conjugate comprises an enzyme, further administering to said patient**

**1) a prodrug, when said enzyme is capable of converting said prodrug to a drug at the target site; or**

**2) a drug which is capable of being detoxified in said patient to form an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or**

**3) a prodrug which is activated in said patient through natural processes and is subject to detoxification by conversion to an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or**

**4)]** administering to said patient a second targetable conjugate which comprises a carrier portion **[which]** and a prodrug, wherein said carrier portion comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment**[, and a prodrug, when said enzyme is capable of converting said prodrug to a drug at the target site]**.

16. (Amended) The method of claim 1, wherein said **first or second** targetable conjugate comprises a peptide.

17. (Amended) The method of claim 1, wherein said **first or second** targetable conjugate comprises a carbohydrate.

18. (Amended) The method of claim 1, wherein said **first or second** targetable conjugate comprises one or more haptens.

19. (Amended) The method of claim 1, wherein said **first or second** targetable conjugate comprises one or more chelators or metal-chelate complexes.

20. (Amended) The method of claim 1, wherein said bi-specific antibody or antibody fragment further comprises a **detectable** radionuclide.

30. (Amended) A kit useful for treating **[or identifying]** diseased tissues in a patient comprising:

(A) a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate;

(B) a first targetable conjugate which comprises a carrier portion **[which] and one or more conjugated enzymes, wherein said carrier portion** comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment**[, and one or more conjugated therapeutic or diagnostic agents, or enzymes]**; and

(C) optionally, a clearing composition useful for clearing non-localized antibodies and antibody fragments; and

(D) **[optionally, when said first targetable conjugate comprises an enzyme,**

**1) a prodrug, when said enzyme is capable of converting said prodrug to a drug at the target site; or**

**2) a drug which is capable of being detoxified in said patient to form an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and,**

**therefore, of increasing the toxicity of said drug at the target site, or**

**3) a prodrug which is activated in said patient through natural processes and is subject to detoxification by conversion to an intermediate of lower toxicity, when said enzyme is capable of reconverting said detoxified intermediate to a toxic form, and, therefore, of increasing the toxicity of said drug at the target site, or**

**4)]** a second targetable conjugate which comprises a carrier portion **[which]** **and a prodrug, wherein said carrier portion** comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment**[, and a prodrug, when said enzyme is capable of converting said prodrug to a drug at the target site]**.